Ibrutinib (Imbruvica) with R-CHOP for diffuse large B-cell lymphoma – first line

LAY SUMMARY

Lymphoma is a cancer of the lymphatic system, which is part of the immune system. It contains cells called lymphocytes that fight infections. Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma. It can occur at any age but is more common in those over 65 years of age.

Ibrutinib is a new drug for diffuse large B-cell lymphoma. It comes in the form of capsules that are taken by mouth and swallowed. Some studies have suggested that this drug may be helpful for people with a particular type of diffuse large B-cell lymphoma who have not yet received any chemotherapy for this disease. A study is now running and is aiming to find out how well ibrutinib works alongside chemotherapy and whether it is safe to use.

If ibrutinib is licensed for use in the UK, it could be a new treatment option for diffuse large B-cell lymphoma that may improve survival.

NIHR HSRIC ID: 9452
TARGET GROUP


TECHNOLOGY

DESCRIPTION

Ibrutinib (Imbruvica; JNJ54179060; PCI 32765) is a selective Bruton’s tyrosine kinase (Btk) inhibitor. It acts by blocking B-cell antigen receptor signalling, thereby arresting the cell cycle and inducing cell death. As Btk is not found in T-cells, ibrutinib does not affect T-cell receptor signalling. In a phase III clinical trial, ibrutinib was administered orally, at 560mg (4 x 140mg capsules) once daily in combination with R-CHOP (rituximab 375mg/m² administered intravenously (IV), cyclophosphamide 750mg/m² IV, doxorubicin 50mg/m² IV, and vincristine 1.4mg/m² IV administered once on day 1 of each 21-day cycle, and prednisone 100mg administered orally once daily on days 1-5 of each cycle).¹

Ibrutinib is licensed in the EU for the treatment of adult patients with:
- relapsed or refractory mantle cell lymphoma.
- chronic lymphocytic leukaemia (first or second line).
- Waldenström’s macroglobulinaemia.

Very common (≥10%) reported adverse events include pneumonia, upper respiratory tract, skin and urinary tract infections, sinusitis, neutropenia, thrombocytopenia, anaemia, dizziness, headache, haemorrhage, epistaxis, bruising, petechiae, diarrhoea, vomiting, stomatitis, nausea, constipation, rash, arthralgia, musculoskeletal pain, pyrexia and peripheral oedema².

Ibrutinib is also in phase III clinical trials for non-Hodgkin’s lymphoma and pancreatic cancer. It is in phase II clinical trials for hairy cell leukaemia, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, ibrutinib will provide an additional oral treatment option in addition to IV R-CHOP chemotherapy for patients with diffuse large B-cell lymphoma.

DEVELOPER

Janssen-Cilag Limited.

AVAILABILITY, LAUNCH OR MARKETING

Ibrutinib is a designated orphan drug in the EU and USA.
Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for approximately 30-35% of all cases\(^3\). DLBCL behaves in an aggressive fashion and typically presents as a nodal or extra-nodal mass with fast tumour growth associated with systemic symptoms, such as sweats, fatigue and fever\(^4\). In about 40% of cases, DLBCL presents in areas outside lymph nodes, such as the digestive tract, skin, bone, thyroid, and testes\(^4\). The causes of NHL in general, and DLBCL specifically, are unclear, however identified risk factors include infectious agents, immunosuppression, genetic susceptibility, and environmental factors such as exposure to agrochemicals\(^5\).

The crude incidence of DLBCL in the EU is estimated at 3-4 per 100,000 per year, and the incidence increases with age from 0.3 per 100,000 per year in those aged 35-39 years to 26.6 per 100,000 per year in those aged 80-84 years\(^6\). The crude incidence of DLBCL in the UK is 8.2 per 100,000 per year and it affects mainly those over 65 years\(^7\). An estimated 20-25% of DLBCL is non-germinal centre B-cell\(^8\). The one-year survival rate for DLBCL is 65%, and the five-year survival rate is 55%\(^8\).

In England, there were 4,532 cases of DLBCL (ICD-10 C83.3) recorded in 2013\(^9\). In the same year, there were 670 deaths from DLBCL registered in England and Wales (ICD-10 C83.3)\(^10\). In 2013-14, there were 32,418 admissions for DLBCL (ICD-10 C83.3) in England, resulting in 78,110 bed days and 35,429 finished consultant episodes\(^11\). Research suggests that more than 30% of patients with DLBCL who initially respond to therapy will ultimately relapse\(^8\).
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

- European Society for Medical Oncology. ESMO Consensus Guidelines: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukaemia (CLL). 201313.
- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 20156.

CURRENT TREATMENT OPTIONS

Treatment regimens for patients with DLBCL are based on individual International Prognostic Index (IPI) scores and age17. DLBCLs have a high cure rate with both initial and conventional dose salvage chemotherapy, with around 50% of patients responding to primary therapy with chemotherapy and rituximab type regimens18. However, long-term survival is low in patients with high IPI risk scores and these individuals have a greater tendency to relapse following treatment19.

- For young (<61 years of age) high and high-intermediate-risk patients – six to eight cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy combined with eight doses of rituximab given every 21 days (R-CHOP21) is the most commonly used treatment regimen6. CHOP chemotherapy with rituximab given every 14 days (R-CHOP14) is also an option for such patients6.
- In patients aged 60 to 80 years – eight cycles of R-CHOP21 is the current standard treatment. Six cycles R-CHOP14 with two additional cycles of rituximab is also an option for this patient group6.
- In patients older than 80 years – six cycles of rituximab combined with attenuated CHOP chemotherapy (R-miniCHOP21) is recommended6. For patients with cardiac dysfunction
or otherwise unfit, doxorubicin may be substituted with gemcitabine\(^b\), etoposide or liposomal doxorubicin, or omitted, from the beginning of treatment or after the first few cycles\(^6\). A pre-chemotherapy phase, where a single injection of vincristine and seven days of oral prednisone is administered, may be utilised in order to reduce toxicity in elderly patients\(^18\).

- In relapsed or refractory disease, some patients with generally good health who respond to salvage chemotherapy may be offered stem cell transplantation (SCT) after high-dose chemotherapy\(^20\). Allogeneic SCT offers a potential cure for DLBCL, but carries a higher risk than autologous SCT\(^20\).

Central nervous system (CNS) prophylaxis (intrathecal or IV high-dose methotrexate) is recommended for certain groups of patients with a high risk of CNS relapse\(^6\,\(^c\).

### EFFICACY and SAFETY

| Trial | NCT01855750, CR102118, PCI-32765DBL3001, U11111-1139-6222, 2013-000959-40; ibrutinib vs placebo, both in combination with R-CHOP; phase III. |
|———|———|
| Sponsor | Janssen-Cilag. |
| Status | Ongoing. |
| Source of information | Trial registry\(^1\). |
| Location | EU (incl UK), USA, Canada and other countries. |
| Design | Randomised, placebo-controlled. |
| Participants | n=800 (planned); aged ≥18 years; non-germinal centre B-cell type DLBCL; stage II-IV; no prior treatment; Eastern Cooperative Oncology Group performance status 0-2. No known CNS or primary mediastinal lymphoma; no prior history of indolent lymphoma; not requiring anticogulation therapy, or requiring treatment with strong CYP3A inhibitors; no prior anthracycline use ≥150mg/m\(^2\). |
| Schedule | Randomised to: ibrutinib 560mg, or matched placebo tablets both administered orally once daily and in combination with rituximab 375mg/m\(^2\) administered IV, cyclophosphamide 750mg/m\(^2\) IV, doxorubicin 50mg/m\(^2\) IV, and vincristine 1.4mg/m\(^2\) IV all administered once on day 1 of each 21-day cycle, and prednisone (or equivalent) 100mg oral once daily on days 1-5 of each cycle. |
| Follow-up | Treatment administered until disease progression, unacceptable toxicity or study completion. Follow-up up to 7 years. |
| Primary outcome/s | Event free survival. |
| Secondary outcome/s | Progression-free survival; overall survival; complete response rate; time to worsening symptoms in the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)\(^c\); pharmacokinetics; and adverse events. |
| Expected reporting date | Study completion date reported as June 2020. |

### ESTIMATED COST and IMPACT

### COST

A pack of 90 x 140mg ibrutinib tablets costs £4,599\(^21\).

\(^b\) Expert personal communication.

\(^c\) FACT-Lym is a health questionnaire.
## Impact - Speculative

### Impact on Patients and Carers
- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other:
- ☐ No impact identified

### Impact on Health and Social Care Services
- ☐ Increased use of existing services
- ☑ Decreased use of existing services: *the company note that patients can receive ibrutinib in outpatient clinics thus reducing the need for inpatient treatments.*
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other:
- ☐ None identified

### Impact on Costs and Other Resource Use
- ☑ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☐ Other reduction in costs:
- ☐ Other:
- ☐ None identified

### Other Issues
- ☐ Clinical uncertainty or other research question identified:
- ☑ None identified

---

### References